



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Stephen R. Auten
Vice-President, Legal – Intellectual Property
Sandoz, Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540

MAR 15 2010

Re: Docket No. FDA-2009-P-0411

Dear Mr. Auten:

This letter responds to your citizen petition, received on August 25, 2009 (Petition), requesting that the Food and Drug Administration (FDA or Agency) refrain from granting final approval for any abbreviated new drug application (ANDA) for a generic version of Actos (pioglitazone hydrochloride (HCl)) tablets and/or Actoplus Met (pioglitazone HCl and metformin HCl) tablets, if the ANDA includes a section viii statement pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)(2)(A)(viii)) with regard to U.S. Patent No. 5,965,584 (the '584 patent) and/or U.S. Patent No. 6,329,404 (the '404 patent), unless that ANDA also includes a paragraph IV certification pursuant to section 505(j)(2)(A)(vii)(IV) of the Act to the respective patent. We have carefully considered the Petition and comments submitted to the docket. For the reasons described below, the Petition is granted.

I. BACKGROUND

A. Actos and Actoplus Met

Actos was approved by FDA on July 15, 1999, and is sold in the United States as 15-, 30-, and 45-milligram (mg) tablets. Actoplus Met was approved by FDA on August 29, 2005, and is sold in the United States as 15-mg/500-mg and 15-mg/850-mg pioglitazone HCl/metformin HCl tablets. Takeda Global Research and Development Center, Inc. (Takeda) holds approved new drug application (NDA) 21-073 for Actos, and NDA 21-842 for Actoplus Met.

B. The '584 and '404 Patents

On November 5, 1999, Takeda submitted the then newly-issued '584 patent for listing in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) in conjunction with its already approved application for Actos. On January 3, 2002, Takeda submitted the then newly issued '404 patent for listing in the Orange Book in conjunction with the same application. When submitted, Takeda's patent declarations

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for the '584 and '404 patents each stated that the patents claimed both the drug product and a method of use. The patent declarations for these patents were timely submitted and were determined to otherwise comply with applicable regulations.¹ However, at the time they were submitted, FDA's Orange Book database lacked the technological capacity to display a single patent as claiming more than one aspect of the drug. At that time, FDA's practice was to display a patent that had been submitted as claiming both a drug product and a method of use only for the method of use for which it had been submitted. Thus, FDA's Orange Book lists each patent as claiming only a method of use and provides a use code for each patent to identify the use for which it was submitted by Takeda. To alert users to the limitations of patent listings for patents submitted before August 2003, and make them aware that the Orange Book may not describe the complete universe of patent claims to which an ANDA applicant must certify, the Orange Book includes a notation that "[p]atents listed prior to August 18, 2003 are flagged with method-of-use claims only as applicable and submitted by the sponsor" and that "[t]hese patents may not be flagged with respect to other claims which may apply" (footnote 2 to the patent and exclusivity list for the Orange Book).

In June, 2003 FDA issued a final rule clarifying the requirements for patent submissions and listing (Patent Listing Final Rule).² The Patent Listing Final Rule requires applicants to identify on FDA Form 3542 patents that cover the approved drug substance, drug product, and/or methods of use, and to verify under penalty of perjury that, among other things, the patent declaration represents "an accurate and complete submission of patent information" (21 CFR 314.53(c)(2)(i)(Q)). By August 18, 2003, the effective date of the Patent Listing Final Rule, the technological capabilities of the Orange Book database had been increased and FDA had the ability to display the fact that a single patent had been submitted as claiming more than one aspect of a drug product. Thus, after that date, when a patent was submitted as claiming more than one aspect of a drug product, the Orange Book displayed the multiple types of claims (drug product, drug substance, and/or method of use) for which a patent had been submitted. FDA did not, however, revisit Orange Book listings for patents submitted before the Patent Listing Final Rule's

¹ Under the applicable regulations at the time of patent submission (1999 and 2002 for the '584 and '404 patents, respectively), a sponsor was required to submit the patent number and date of expiration (21 CFR 314.53(c)(1)(i)), the type of patent (21 CFR 314.53(c)(1)(ii)), the name of the patent owner (21 CFR 314.53(c)(1)(iii)), and the name of a U.S. agent if the patent owner or applicant resides outside of the United States (21 CFR 314.53(c)(1)(iv)). In addition, for formulation, composition, and method-of-use patents, the NDA applicant or NDA sponsor was required to submit a declaration that stated

The Undersigned declares that Patent No. ____ covers the formulation, composition and/or method of use of (*name of drug product*). This product is (*currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act*) [or] (*the subject of this application for which approval is being sought*):

21 CFR 314.53(c)(2) (emphasis in original).

² FDA, Final Rule, Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed (Patent Listing Final Rule) (68 FR 36676, June 18, 2003).

effective date but, instead, retained the disclaimer regarding the incomplete Orange Book listing for such patents.

Thus, although Takeda submitted the '584 and '404 patents to the Actos NDA as patents containing drug product and method-of-use claims, these patents to date are flagged in the Orange Book listing for Actos only with respect to the method-of-use claims because they were submitted before August 18, 2003.³

C. Statutory and Regulatory Requirements

The Act and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. The Act and FDA regulations also require that a sponsor of an NDA submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product described in the NDA. Specifically, section 505(b)(1) of the Act (21 U.S.C. 355(b)(1)) requires NDA applicants to file as part of the NDA:

the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.⁴

As noted in footnote 1 of this letter, before 2003 the regulations required the NDA holder submit certain information regarding each submitted patent, including the type of patent and expiration date and a declaration that the patent claimed the formulation, composition, and/or method of using the drug. Since their revision in 2003, the regulations have provided that NDA applicants must submit the required information on FDA Form 3542, which includes space for submitting a single patent as claiming multiple aspects of an approved drug product. FDA is required to publish certain patent information for patents claiming drugs approved under section 505(c) and does so in the Orange Book (section 505(b)(1), (c)(2), and (j)(7) of the Act and 21 CFR 314.53(e)).

A drug product with an effective approval under section 505(c) of the Act is known as a

³ The '584 patent as listed for Actoplus Met is flagged in the Orange Book as claiming both a drug product and a method of use. This patent was submitted for listing for Actoplus Met after August 18, 2003, and thus the Orange Book more accurately reflects both types of claims for which the NDA holder submitted it. The '404 patent is not listed for Actoplus Met.

⁴ Section 505(c)(2) of the Act imposes an additional patent submission requirement on holders of approved NDAs when those holders subsequently obtain new patent information that could not have been submitted with the NDA.

listed drug.⁵ Under provisions added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Public Law No. 98-417, 98 Stat. 1585, the Act permits submission of ANDAs for approval of generic versions of listed drugs (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling), and that its product is bioequivalent to the listed drug.

Each ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail in the following subsection, the timing of ANDA approval depends on, among other things, the intellectual property protections for the listed drug the ANDA references and whether the ANDA applicant challenges those protections (see section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the Act).⁶ In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights.

1. *Paragraph I-IV Certification*

With respect to each patent (or patent claim) which claims a listed drug and is submitted by the sponsor for listing in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

- (I) That the required patent information relating to such patent has not been filed (paragraph I certification)
- (II) That such patent has expired (paragraph II certification)
- (III) That the patent will expire on a particular date (paragraph III certification)
- (IV) That such patent is invalid or will not be infringed by the drug for which approval is being sought (paragraph IV certification)

⁵ Under 21 CFR 314.3(b), "[l]isted drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified in the Orange Book as having an effective approval. The Orange Book also includes patent information for each approved drug (§ 314.53(e)).

⁶ Relevant intellectual property protections affecting the timing of ANDA approval include marketing exclusivity and listed patent protection for the listed drug. Marketing exclusivity for the listed drug is not at issue here.

The purpose of these certifications is “to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible” (*Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003)).

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking full effective approval of its ANDA.

If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA, the applicant must submit a paragraph IV certification to FDA. The applicant filing a paragraph IV certification must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal bases for the applicant’s opinion that the patent is invalid or not infringed (see section 505(b)(2)(B) and (j)(2)(B) of the Act).

The filing of a paragraph IV certification “for a drug claimed in a patent or the use of which is claimed in a patent” is an act of patent infringement (35 U.S.C. 271(e)(2)(A)). If the patent owner or NDA holder brings a patent infringement suit against the ANDA applicant within 45 days of the date it received notice of the paragraph IV certification, the approval of the ANDA will be stayed for 30 months from the date of such receipt by the patent owner and NDA holder, unless a court decision is reached earlier in the patent case or the patent court otherwise orders a longer or shorter period (see section 505(c)(3)(C) and (j)(5)(B)(iii) of the Act). When the 30 months have expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of a paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

As a reward for challenging a patent and potentially clearing the way for generic competition, the first ANDA applicant who submits a paragraph IV certification to a patent is eligible for 180 days of marketing exclusivity. When an ANDA applicant with a paragraph IV certification is eligible for this exclusivity, the exclusivity generally prohibits FDA from approving any subsequent ANDA with a paragraph IV certification to that patent before the triggering of and during the exclusivity period (21 U.S.C. 355(j)(5)(B)(iii)-(iv) (2002))⁷.

2. Section viii Statement

⁷ Congress amended 21 U.S.C. 355(j) in late 2003 (see the Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (MMA) (Dec. 8, 2003)). The majority of the amendments pertaining to 180-day exclusivity do not apply to the exclusivity determinations for the Actos ANDA because the earliest ANDA containing a paragraph IV certification was submitted before the December 8, 2003, enactment date of the MMA.

The paragraph I, II, III, and IV certifications are not the only manner in which an ANDA applicant may address all relevant patents (or patent claims). When a patent is listed only for a method of use, an ANDA applicant seeking to omit from its labeling that approved method of use covered by the listed patent need not file a paragraph I to IV certification for that patent. Instead, the applicant may submit a *section viii statement* acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval (see section 505(j)(2)(A)(viii) of the Act). Specifically, section 505(j)(2)(A)(viii) of the Act provides the following:

if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use.

If an applicant submits such a statement, that ANDA applicant must omit from its labeling information pertaining to the protected use (21 CFR 314.92(a)(1) and 314.94(a)(12)(iii)).⁸ If an ANDA applicant files a section viii statement to a patent that protects only a method of use (and makes the requisite labeling carveout), the patent claiming the protected method of use will not serve as a barrier to ANDA approval nor will 180-day exclusivity with respect to that patent serve as such a barrier.

FDA implementing regulations at 21 CFR 314.94(a)(12)(iii) describe the applicability of the section viii statement as follows:

If patent information is submitted under section 505(b) or (c) of the [A]ct and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.

Accordingly, FDA regulations also expressly recognize that an application that does not seek approval for a condition of use claimed by a listed patent may omit that condition of use from its labeling by submitting a section viii statement.⁹

⁸ See also H.R. Rep. No. 857 (Part I), 98th Cong., 2d sess. 21.

...The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication.

⁹ Such an applicant must demonstrate that the differences in labeling render its proposed drug product no less safe and effective than its listed drug for the remaining, nonprotected conditions of use (21 CFR 314.127(a)(7)).

Section 505(j)(2)(A)(viii) of the Act and the implementing FDA regulations (21 CFR 314.94(a)(12)(iii)) allow a section viii statement only for patent claims that describe a method of use. Thus, where a patent is submitted as including both method-of-use and other claims (such as drug product claims), the section viii statement would be inapplicable to the other patent claims.¹⁰ For drug product claims, an ANDA applicant would be required to submit the appropriate certification under section 505(j)(2)(A)(vii) of the Act. Therefore, under the Act, a section viii statement alone would be insufficient to meet the statutory patent certification requirement where the NDA holder submitted an acceptable patent declaration that requested that FDA list the patent as including drug product claims in addition to method-of-use claims.

The Agency has previously explained that a paragraph IV certification and a section viii statement “are not overlapping, and an applicant does not have the option of making a certification under § 314.94(a)(12)(i)(A)(4) in lieu of, or in addition to, a statement under § 314.94(a)(12)(iii)” (see FDA, Final Rule, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions (59 FR 50338 at 50347 (October 3, 1994)). The Agency further noted (at 50347):

If, however, there are listed patents that present both a product and method of use claim, the applicant may file a paragraph IV certification with respect to the product patent or patent claim and a statement that the product that is the subject of the application does not involve a patented method of use with respect to the method of use patent or patent claim.

Thus, where a patent is submitted as claiming both the drug product and a method of using the drug, if a sponsor does not seek approval for the method of use claimed by the patent but seeks approval of the drug product for a different use before the patent expires, FDA’s practice is to allow a *split* certification to that patent, which includes both a paragraph IV certification to the drug product claim and a section viii statement to the method of use and an accompanying labeling carveout. When a patent is listed with multiple method-of-use claims, FDA permits an applicant to submit a split certification with a paragraph IV certification to a method of use for which the applicant seeks approval and a section viii statement for a method of use the applicant seeks to carve out from its labeling. In either case, the ANDA applicant must address all claims for which the patent was submitted and may file a paragraph IV certification to some claims and a section viii statement to other claims, as appropriate (see Repaglinide Citizen Petition Response, Docket Nos. FDA-2008-P-0343 and -0411 (December 4, 2008) (Repaglinide Citizen Petition Response) at 18). This approach preserves the NDA holder’s statutory

¹⁰ As noted in section I.B of this letter, for patents submitted after August 18, 2003, the requisite patent listing forms required an NDA holder to identify whether a patent claimed a drug product, drug substance and/or method of use and the Orange Book should accurately reflect what the NDA holder has submitted. However, for patents submitted before August 18, 2003 (such as the ‘584 and ‘404 patents), the Orange Book may not accurately reflect that a single patent was submitted as claiming more than one aspect of a drug and includes a footnote alerting Orange Book users to this limitation. FDA recognizes that this has led to some confusion among ANDA applicants, and is separately considering whether and how to more accurately reflect in the Orange Book the multiple aspects of a drug for which certain patents were submitted before August 18, 2003.

right to defend its patent rights prior to ANDA approval while permitting the ANDA applicant to exercise its statutory right to seek approval for fewer than all of the approved conditions of use.

II. ANALYSIS

In the Petition, you assert that although the Orange Book does not accurately reflect that the '584 and '404 patents include both drug product and method of use claims, a split certification (a paragraph IV certification and a section viii statement) is required for any pending ANDA for a generic version of Actos and/or Actoplus Met tablets that includes a section viii statement with regard to the '584 patent and/or the '404 patent. You assert that because the Orange Book listings of the '584 and '404 patents with respect to Actos predate the August 18, 2003 effective date of FDA's current patent listing regulation (21 CFR 314.53), the Orange Book listings for those patents do not indicate whether, in addition to the use claims identified, each patent also includes a drug substance claim, a drug product claim, or both (Petition at 4). However, relying on statements in complaints filed by Takeda in the U.S. District Court for the Southern District of New York against other generic applicants for allegedly infringing the '584 and/or '404 patents, you assert that Takeda has characterized both patents as including drug product claims in addition to the method-of-use claims identified in the Orange Book that can be asserted with respect to Actos and/or Actoplus Met (Petition at 4-5, 10-11). Accordingly, it is your position that the Agency need not determine whether the '584 and '404 patents include drug product claims because Takeda has already acknowledged that both patents include such claims, and that the Agency may of its own accord flag the '584 and '404 patents as listed for Actos as including drug product claims (Petition at 11). You thus conclude that FDA should require any pending ANDAs referencing Actos and Actoplus Met to include a split certification to both patents (Petition at 1, 2, 11).

You state that absent the relief sought, ANDA applicants who file a section viii statement to the method-of-use claims and who do not separately address the drug product claims in the '584 and '404 patents would be able to impermissibly bypass applicable law and regulations requiring a paragraph I-IV certification to patent claims that do not claim a method of use. You state that this result would allow ANDA applicants to circumvent 180-day exclusivity and thereby significantly disadvantage other ANDA applicants for generic versions of Actos tablets (and/or Actoplus Met tablets), such as Sandoz, Inc. (Sandoz), whose ANDAs include an appropriate split certification.

In a Comment to this Petition submitted on January 22, 2010, Takeda states that it has previously requested that FDA contact any ANDA applicants that may have submitted only section viii statements regarding one or both of these patents and direct the applicants to submit appropriate patent certifications (Comment to Citizen Petition by Takeda, Docket No. FDA-2009-P-0411 (January 22, 2010) (Takeda Comment)). Enclosed with the Takeda Comment is a letter referencing NDA 21-073 submitted by Takeda to FDA (November 23, 2009) (Letter). In the Takeda Comment and Letter, Takeda states that when it first submitted the '584 and '404 patents to FDA for listing with respect to Actos in 1999 and 2002, respectively, it characterized the patents in the

appropriate patent declarations as containing both drug product and method-of-use claims (Takeda Comment at 1, referencing Letter at 1-3, and original patent submissions by Takeda in 1999 and 2002). In the Comment, Takeda reconfirms “the listing of [the ‘584 and ‘404 patents], under the terms described in Takeda’s original patent submissions” (Comment at 1). Specifically, Takeda states in its original patent declarations (attached to its Comment) that it characterized each patent as “containing both ‘Drug Product’ and ‘Method of Use’ claims.” Takeda notes that “the ‘584 patent claims both pharmaceutical compositions comprising an insulin sensitivity enhancer in combination with a biguanide, as well as methods for treating diabetes comprising administering a therapeutically effective amount of an insulin sensitivity enhancer in combination with a biguanide” (Comment at 1). Takeda also states that “the ‘404 patent claims both pharmaceutical compositions comprising an insulin sensitivity enhancer in combination with an insulin secretion enhancer, as well as methods for treating diabetes comprising administering a therapeutically effective amount of an insulin sensitivity enhancer in combination with an insulin secretion enhancer” (Comment at 1).

FDA’s role in listing patents and patent information in the Orange Book is ministerial (see *American Bioscience v. Thompson*, 269 F.3d 1077, 1080 (D.C. Cir. 2001)). FDA relies on the NDA sponsors to provide an accurate patent submission (consistent with previously applicable regulations regarding patent submissions for patents submitted before August 18, 2003 and on FDA Form 3542 for patents submitted after August 18, 2003). FDA will assess patents only to determine whether FDA’s requirements for listing have been met. If an ANDA applicant questions the accuracy or completeness of patent listings, the regulations at 21 CFR 314.53(f) provide a process for challenge to a patent listing. Under this process, FDA will forward the challenge to the NDA holder; however, if the NDA holder confirms the accuracy and completeness of its listing, FDA will not second guess the NDA holder and the patent remains listed. Although you have not availed yourself of this process, consistent with its ministerial role, FDA will not independently consider your assertion that statements in a complaint Takeda filed in the U.S. District Court for the Southern District of New York against Teva serve as evidence that the ‘584 and ‘404 patents cover both method-of-use and drug product claims for Actos (Petition at 4-5). Both before and after August 18, 2003, it is the patent declaration submitted by the NDA holder and any subsequent amendments or supplements to that declaration that controls FDA’s listing of patents and patent information.

In keeping with our practice of relying solely on the NDA sponsor’s patent declaration describing relevant patent claims in Orange Book-listed patents, FDA will rely on Takeda’s patent declarations submitted to FDA. We have evaluated our records and confirmed that Takeda’s original patent declaration to FDA for the ‘584 and ‘404 patents stated that the patents included drug product claims and method-of-use claims. Had those patent declarations been submitted after August 18, 2003, consistent with its ministerial duties and the increased technological capabilities of the Orange Book database, FDA would have included in the Orange Book listing for Actos drug product claims in addition to the method-of-use claims.

Under the plain language of the statute, the patent certification requirement is not triggered by the publication in the Orange Book of patent information submitted to FDA. Rather, as noted above, the statute requires certification where the patent (or patent claim) claims a listed drug, and where the NDA holder is required to submit and has submitted that patent information to FDA. This obligation to certify attaches regardless of whether that submission is accurately reflected in the Orange Book.¹¹ Thus, the pre-2003 technological limitations that prevented our Orange Book listings from reflecting the fact that Takeda submitted the patents as claiming both a drug product and a method of using that drug product do not limit Takeda's rights to receive patent certifications for the drug product claims in the '584 and '404 patents (see *Teva Pharmaceuticals v. Leavitt*, 548 F.3d 103, 108 (D.C. Cir. 2008) ("[T]he Agency's failure to list a patent after the NDA holder provided the information would not deprive the branded drug manufacturer of its rights under paragraph IV.")). Nor does the absence of the drug product information in the Orange Book deprive the eligible ANDA applicant with the first paragraph IV certification with respect to the patent of eligibility for a 180-day exclusivity period (see *id.* at 107 ("Inadvertent failure by the agency to meet its separate publication requirement cannot defeat facts.")).

Although the '584 and '404 patents are flagged in the Orange Book listing for Actos only with respect to method-of-use claims, the Orange Book specifically informs users that patents listed prior to August 18, 2003 "may not be flagged with respect to other claims which may apply" (footnote 2 to the patent and exclusivity list for the Orange Book). In the narrow case where the Orange Book listings are inaccurate because of technological limitations that prevented a single patent from being displayed as claiming more than one aspect of a drug product, the flagging of method-of-use patents as such (and the corresponding existence of use codes) are intended only to alert ANDA applicants to the existence of a patent that claims an approved use; they are not meant to imply the existence or nonexistence of any additional drug substance or drug product claims for which the patent was submitted and for which a certification is required. Even though the Orange Book flags only the method-of-use claim with regard to submissions made before August 18, 2003, a split certification is appropriate where, as here, the NDA holder's submission of patent information included both method-of-use claims and drug product claims. FDA and ANDA applicants cannot ignore drug product claims submitted to FDA by the NDA holder, even if they are not reflected in the Orange Book.

In the Repaglinide Citizen Petition Response, FDA confirmed that for patents that are submitted as claiming both a drug product and a method of use, if an ANDA applicant chooses to submit a section viii statement with respect to any method-of-use claims, the applicant must also submit an appropriate certification under section 505(j)(2)(A)(vii) of the Act for any drug product claims (Repaglinide Citizen Petition Response at 18). Similarly, if an ANDA applicant submits an application referencing Actos or Actoplus Met that addresses only the method-of-use claims (by including a section viii statement with respect to the '584 and/or '404 patents), the applicant would also need to address the

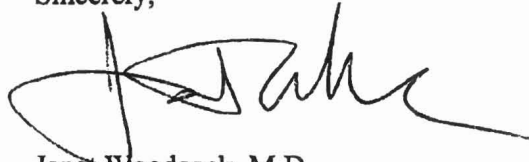
¹¹ See FDA, Proposed Rule, Abbreviated New Drug Application Regulations (54 FR 28872 at 28885 (July 10, 1989) ("The patent information submitted to FDA, whether or not published in [the Orange Book], should be the basis of the applicant's certification")).

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drug product claims in those patents by submitting an appropriate certification to each respective patent under section 505(j)(2)(A)(vii) of the Act. FDA will consider any ANDA referencing Actos that lacks appropriate certifications to the '584 and '404 patents ineligible for final approval. Likewise, FDA will consider any ANDA referencing Actoplus Met that lacks an appropriate certification to the '584 patent ineligible for final approval.

Therefore, for the reasons described, the Petition is granted.

Sincerely,

A handwritten signature in black ink, appearing to read 'Janet Woodcock', with a large, stylized initial 'J'.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research